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RESEARCH ARTICLE

An Inflammation-related Nutrient Pattern is Associated with Both Brain and Cognitive Measures in a Multiethnic Elderly Population

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Abstract: ***Background:*** Accumulating evidence suggests that dietary factors are associated with Alzheimer's disease, and brain and cognitive health. It is however unclear whether inflammation explains this association.

Objective: To examine whether an inflammation-related nutrient pattern (INP) was associated with neuroimaging and cognitive measures of brain health.

Method: The current cross-sectional study included 330 non-demented elderly (mean age 79 years at MRI scan) participants in a multi-ethnic, community-based cohort study who had information on nutritional intake (estimated from food frequency questionnaire), circulating C-reactive protein and interleukin-6 (measured by ELISA), MRI scans, and cognition. Diet and blood samples were collected approximately 5.3 years prior to the MRI and cognitive test visit. We used a reduced rank regression model to derive an INP based on 24 nutrients' relationship with CRP and interleukin-6. We examined the association of the INP with brain and cognitive measures using regression models adjusted for age, sex, race/ethnicity, education, caloric intake, APOE genotype, body mass index, and vascular burden, as well as intracranial volume for the brain MRI measures.

Results: The INP was characterized by low intake (effect loading <-0.15) of calcium, vitamins (D, E, A, B1, B2, B3, B5, B6), folate, Ω-3 poly-unsaturated fatty acids, and high intake (>0.15) of cholesterol. As designed, this INP was positively correlated with CRP (Pearson's r=0.25 p=0.005) and interleukin-6 (r=0.30, p<0.0001). Each unit increase in INP was associated with 36.8 cm^3 (p=0.023) smaller total brain volume and 0.21 (p=0.038) lower visuospatial z-score. Mediation analysis showed that TGMV (b=0.002, p=0.003) was associated with visuospatial cognitive function, and there was a significant mediation effect by TGMV (indirect effect: -0.049, 95% CI: -0.1121 ~ -0.0131) for the association between INP on visuospatial cognitive score.

Conclusions: Among older adults, a diet with high inflammatory potential is associated with less favorable brain and cognitive health.

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1. INTRODUCTION

Accumulating evidence suggests that diet may play an important role in the prevention of sporadic, late-onset form of Alzheimer's disease (AD) [1, 2]. Our previous work from the Washington Heights, Hamilton Heights, and Inwood Columbia Aging Project (WHICAP), a longitudinal population-based cohort in Manhattan, indicated that adherence to a Mediterranean-type diet (MeDi) [3] or other healthy dietary patterns [4] was related with decreased risk for AD. Furthermore, we found that, among non-dementia old adults, such diets were also associated with brain volumes and cognitive performances [5, 6], two strong predictors for subsequent AD [7]. However, the underlying biological mechanisms for a potentially protective effect of these diets remain unclear.

Among all potential mechanisms, an inflammation pathway might be one of the important ones. Evidence on the biological effects of individual nutrients or foods suggests that many of them can modulate inflammatory responses [8]. Meanwhile, strong evidence suggests the involvement of systemic inflammation in AD or AD-related brain and cognitive decline [9]. Nevertheless, few studies have evaluated the inflammatory pathway for diet-AD association. We previously found that CRP did not explain the association be-

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tween MeDi and lower risk of AD [10]. While further examination of inflammation in MeDi-AD association is warranted, there might exist other aspects or combinations of foods that are more closely related with inflammatory biomarkers. Reduced-rank regression (RRR) model using inflammatory markers as response variables can facilitate the identification of dietary patterns that are designed to be most closely associated with inflammation [2, 4, 11]. To date, only one study used RRR with interleukin-6 (IL6) as the response variable and found an IL6-related dietary pattern predicted rate of decline in reasoning cognition [12]. Two other studies used dietary inflammatory scores, based on *a priori* defined inflammatory impact of each dietary components, but the results were inconsistent [13, 14]. Moreover, despite the strong implications for brain MRI findings in preclinical AD [7], no study has examined the role of inflammation in the relation between diet and brain measures.

In the current study, we examined whether an inflammation-related nutrient pattern (INP) was associated with brain and cognition measures among elderly participants of the community-based multi-ethnic WHICAP cohort. We further examined whether the relationship of this INP and cognition can be explained by brain measures.

2. MATERIALS AND METHODS

2.1. Study Participants

Participants of the WHICAP were identified from a probability sample of elderly Medicare beneficiaries (≥65 years) residing in northern Manhattan. Participants received comprehensive demographic, lifestyle, and medical assessments at baseline and were followed every 18 months [15]. The diagnosis of dementia and its subtypes, as well as mild cognitive impairment (MCI), were based on standard research criteria [16], using all available information at a consensus conference. Among the 680 non-demented participants of the neuroimaging sub-study, which started in 2004 among ongoing WHICAP participants [17], 508 (75%) and 435 (66%) subjects had CRP and IL6 measured, respectively, and 405 had both biomarkers measured. Additionally, IL6 level was out of detection limit for 68 subjects, and 7 subjects had no dietary information assessed. The final analytical sample included a total of 330 subjects who had both CRP and IL6 circulating levels available.

2.2. Standard Protocol Approvals, Registrations, and Patient Consents

The Columbia University Institutional Review Board reviewed and approved this project. All participants provided written informed consent.

2.3. Dietary Information

Information about average diet over the prior year was obtained using the 61-item version of Willett's semi-quantitative food frequency questionnaire (Channing Laboratory, Cambridge, MA), administered by trained interviewers in English or Spanish. The validity (using two 7-day food records as the criterion) and reliability (using two SFFQs administered 2 months apart) of various components of the questionnaire were fair to good, with intraclass correlations generally above 0.3 [18-20]. We have also previous shown the dietary habits in general were stable among the study population over time [3, 4]. The daily intake of nutrients was computed by multiplying the consumption frequency of each food item by the nutrient content of the specified portion of the food item.

2.4. Biomarker Measurement

The non-fasting blood samples were processed as previously described [21]. Blood samples used for the biomarker measures were collected on (86%) or after (14%, on average 7.4 years after) the visit as the baseline dietary assessment. High sensitivity CRP plasma levels were measured using ELISA (Diagnostic systems laboratories, INC, Texas), with sensitivity, the intra-assay coefficient of variation (CV), and inter-assay CV of 1.6 ng/ml, 4.6%, and 11.7%, respectively. The serum IL-6 levels were measured in duplicate using high sensitivity quantitative sandwich enzyme immunoassay kit (R&D Systems, MN), with sensitivity, intra- and inter-assay CVs of 0.11 pg/ml, 7.4%, and 7.8%, respectively. Laboratory personnel were blinded as to all other information of the subjects. Circulating levels of inflammatory biomarkers were log-transformed.

2.5. MRI Protocol

MRI scans were acquired on a 1.5T Philips Intera scanner at Columbia University Medical Center. The MRI scans were performed on average 4.5 (SD=0.9) years after the blood samples were collected, and 5.3 (SD=2.7) years after the dietary assessment.

Global brain measures including intra-cranial volume (ICV), total brain volume (TBV), total gray matter volume (TGMV), and total white matter volume (TWMV) were calculated from T1-weighted images using Freesurfer (V.5.1) (http://surfer.nmr.mgh.harvard.edu/) [5, 17]. To adjust for differences in head size across participants, regression models were run with ICV as the independent variable and each of the brain volumes as the outcome variable. The regression residuals were used in all the subsequent main analyses. We calculated mean cortical thickness across all regions of interests within each subject. White matter hyperintensity volumes (WMHV) were derived from standard T2-weighted FLAIR images using an intensity-driven algorithm to provide quantitative measurements of WMH volume [22]. WMHV was controlled for head size by taking the ratio and then normalized by log-transformation [$\log_{10}$ (WMHV/ICV)].

2.6. Cognitive Ability

Cognitive ability at the time of MRI scan visit was measured with a neuropsychological battery [15] which was administered either in English (70% of the subjects) or Spanish (30%). Based on an exploratory factor analysis using principal axis factoring and oblique rotation, selected neuropsychological tests scores were combined into four composite scores (memory, language, executive/speed, and visuospatial) [15]. For each of the cognitive measures, z-scores were calculated and then averaged to create a composite z-score for each of the four domains. These factor domain scores

were subsequently averaged to produce a composite 'mean cognition' z-score. A higher z-score indicates better cognitive performance.

2.7. Covariates

To control for potential confounding effects from various factors, we considered continuous variables including age (years), education (years), and body mass index (BMI; kg/m^2). Ethnicity was based on self-report using the format of the 2000 US census, including African American (Black non-Hispanic), Hispanic, White (non-Hispanic) or Other, and was used as a dummy variable with 'non-Hispanic White or Other' as the reference. *APOE-ε4* genotype (presence of either 1 or 2 vs. absence of *ε4* alleles) and sex (female vs. male) were used as dichotomous variables. Stroke was self-reported or from neurological examination or medical records review. Presence or absence of heart disease, diabetes mellitus, and hypertension were based on self-report or use of medications. A composite vascular burden score was calculated by summing up all 4 dichotomous vascular comorbidities scores, ranging from 0-4.

2.8. Statistical Analyses

RRR determines linear combinations (i.e. nutrient pattern to be derived) of a set of predicting variables (nutrients) by maximizing the explained variation of a set of response variables (inflammatory biomarkers) [11]. In this study, RRR was performed using 24 predetermined nutrients (Table **1**) as predicting variables and two inflammatory biomarkers (CRP and IL6) as response variables. The selection of nutrients and biomarkers was based on previous reports of their associations with brain measures and cognitive health, as well as the inflammatory potential of the nutrients. Nutrient intakes were adjusted for caloric intake using the regression residual method, and their standardized residuals were used in the analysis. A higher nutrient pattern score indicates a stronger adherence of a subject's diet to the particular nutrient patterns (NP). According to the RRR method, the number of RRR-derived NP equals the number of response variables entered into the model [11]. Therefore, in total two NPs were derived.

Pearson correlation tests were run to examine the relationship between the nutrient patterns and inflammatory biomarkers. Demographic, clinical, cognitive, and brain morphological characteristics of participants by INP tertiles were compared using ANOVA for continuous variables and χ^2 test for categorical variables.

Generalized Linear Models were used to test whether the nutrient patterns were associated with brain and cognitive measures. The models were adjusted for age (model 1), additionally for sex, education, race/ethnicity, caloric intake, *APOE* genotype, and, for brain measures only, ICV (Model 2), and further adjusted for BMI and vascular factors (Model 3).

We performed a few sensitivity analyses. We excluded 82 subjects with MCI and repeated the analyses on brain measures among cognitively normal subjects only, in order to limit the possibility of reverse causation as well as dietary data recall biases. We examined whether the relationship between INP and brain or cognitive measures differ among different age (younger-old vs. old-old by median age), sex, *APOE*, BMI (median-split), or race/ethnic groups. To test the robustness of the RRR-derived nutrient patterns and their relationship with brain and cognitive measures, we derived a CRP-related NP (CRP-NP) and an IL6-related NP (IL6-NP) by entering CRP or IL6 each as the only response variable in two separate RRR models. We also ran a RRR model with both CRP and IL6 as response variables but with a wider selection of nutrients (32 nutrients in total) which additionally included fiber, zinc, copper, manganese, phospherous, potassim, magnesium, and sodium. We performed mediation analysis [6, 23], adjusted for Model 3 covariates, to see whether the brain measures mediated the association between INP and cognitive ability. Specifically, the mediation model simultaneously estimates the total effect (c) of INP on visuospatial cognitive score, the direct effect of INP on visuospatial cognitive score (c'), the indirect effect of INP on visuospatial cognitive score through TGMV (estimated from the product of path a, INP on TGMV, and path b, TGMV on visuospatial cognitive score). A significant indirect effect (ab) indicates the existence of mediating effect of TGMV on the relationship of INP to visuospatial cognitive score.

All analyses were performed using PASW Statistics 17.0 (formerly SPSS Inc., Chicago, IL USA). All p-values were based on two-sided tests with the significance level set at 0.05.

3. RESULTS

3.1. Missing Data Analysis

Compared to participants who were not included in the current study (n=350) due to missing biomarker or diet information, participants included in the study (n=330) were younger (79.5 vs. 80.6 years, p=0.007) and had a higher percentage of Whites (36% vs. 25%) while lower percentages of African-Americans (32% vs. 38%) or Hispanics (33% vs. 38%) (p=0.001).

3.2. INP Derived from RRR

Two nutrient patterns were derived from the RRR model and they explained 9.26% of the total variation of CRP and IL6. The first nutrient pattern accounted for two-thirds (82%) of explained total variation of CRP and IL6, so in the subsequent analyses we focused on this first nutrient pattern which was renamed as INP. The derived INP was characterized by low intakes (effect loadings <-0.15) of calcium, vitamin D, vitamins E, A, B1, B2, B3, B5, B6, folate, Ω-3 PUFA, and high intake (effect loading >0.15) of cholesterol (Table **1**). As designed by RRR, this INP was positively correlated with CRP and IL-6 (r=0.25 and 0.30, respectively, both p<0.0001), and the correlations did not seem to be confounded by age, sex, ethnicity, education, and BMI (partial correlation adjusted for these variables r=0.24 and 0.28, respectively, both p<0.0001).

3.3. Characteristics of Study Subjects by Tertiles of INP

Compared to those with the lowest tertile of INP, subjects with the highest tertile of INP score were older (p=0.04); had lower education (p=0.014); had larger percent-

Table 1. Factor loadings of nutrients associated with the INP from the reduced rank regression model.

Nutrients in the RRR model[#]	INP*
Pantothenic acid (vitamin B5, mg)	-0.42
Thiamin (vitamin B1, mg)	-0.39
Calcium (mg)	-0.36
Vitamin E (mg)	-0.31
Riboflavin (vitamin B2, mg)	-0.29
Vitamin B6 (mg)	-0.23
Vitamin D (IU)	-0.20
Vitamin A (IU)	-0.18
Total folate (μg)	-0.18
Ω-3 Polyunsaturated fatty acid (g)	-0.16
Niacin (vitamin B3, mg)	-0.16
Vitamin C (mg)	-0.11
β Carotene (μg)	-0.10
β Cryptoxanthin (μg)	-0.09
Total carbohydrates (g)	-0.05
Ω-6 PUFA (g)	-0.03
Iron (mg)	-0.01
Lycopene (μg)	0.01
Total protein (g)	0.03
Lutein (μg)	0.05
Saturated fatty acid (g)	0.07
Monounsaturated fatty acid (g)	0.07
Vitamin B12 (mg)	0.07
Cholesterol (mg)	0.31

[#]The INP was derived with reduced rank regression with both CRP and IL6 entered into the model as the response variables and 24 nutrients as the independent variables. RRR identifies linear functions of predictors (*e.g.,* nutrients) that simultaneously explain as much variation in the responses of interest (*e.g.,* inflammatory markers) as possible.

*Factor loadings represent the magnitude and direction of each food group's contribution to a specific dietary pattern score. A positive factor loading indicates that a higher intake of the nutrient contributes to a higher pattern score, while a negative loading indicates a higher intake of the nutrient contributes to a lower pattern score. Factor loadings <0.15 or > 0.15 are highlighted in bold and indicate the corresponding nutrients are the key nutrients for the INP.

ages of African-Americans and Hispanics and lower percentage of Whites (p<0.0001); had lower language, speed, visuospatial, and mean cognitive scores; and had smaller ICV-adjusted TBV, TGMV, TWMV, and large ICV-adjusted WMHV (Table **2**).

3.4. Associations of the INP with Brain and Cognitive Measures

Each unit increase in INP was associated with 36.8 (p=0.023), 22.9 (p=0.005), and 22.8 (p=0.03) cm^3 smaller TBV, TGMV, and TWMV, respectively, and 0.21(p=0.038) lower visuospatial z-score (Model 3 in Table **3**). For comparison, 10 year increase in age was associated with 22.1 cm^3 smaller TBV, 19.6 cm^3 TGMV, 23.3 cm^3 TWMV, and 0.20 lower visuospatial z-score (all p<0.001).

3.5. Sensitivity Analyses

After excluding 82 MCI subjects, the associations in general remained the same. Adjusted for Model 3 covariates, each unit increase in INP was associated with 19.85 cm^3 (p=0.027) smaller TGMV, 0.30 (p=0.003) lower visuospatial, and 0.28 (p=0.011) lower mean cognitive z-scores.

The difference among the ethnic groups (i.e. p=0.037 for the interaction INP × African-Americans /Whites) was significant for visuospatial cognitive score. In general, the strength of the association between INP and visuospatial cognitive score was similar between Whites (b=-0.22, p=0.05) and Hispanics (b=-0.28, p=0.26), and the INP-TGMV association was also similar between Whites (b=-0.29, p=0.01) and Hispanics (b=-0.30, p=0.04). INP was not associated with visuospatial cognitive score (b=0.23, p=0.21) or TGMV (b=-0.15, p=0.43) among African-Americans. We did not detect any other significant interactions of INP with age group, sex, APOE status, and BMI groups.

We found CRP-NP, IL6-NP, and INP32 (the INP derived from a RRR model with 32 nutrients) were all positively correlated well with the original INP, with r=0.87, 0.88, and 0.84 (p<0.0001 for all), respectively, and with similar dominant nutrients as INP (Table **e1**). The IL6-NP was associated with both TGMV and visuospatial cognitive ability, CRP-NP and INP32 were associated with TMGV but not with visuospatial cognitive ability (Table **e2**).

Mediation analysis showed TGMV (b=0.002, p=0.003) was associated with visuospatial cognitive function, and there was a significant mediation effect by TGMV (indirect effect: -0.049, 95%CI:-0.1121 ~ -0.0131) for the association between INP on visuospatial cognitive score (Fig. **e1**). After taking into consideration the significant paths via TGMV, the effect of INP on visuospatial score was reduced to $\beta c'$= -0.16 (p=0.12).

4. DISCUSSION

In this study of a multiethnic elderly population, we found for the first time that an inflammatory-related nutrient pattern was associated with smaller brain volume, particularly the gray matter volume, as well as worse visuospatial performance. The magnitude of the effect of consuming a diet that yields a 1-unit higher INP score is comparable to that of 10 years of increasing age. Furthermore, accelerated grey matter neurodegeneration might be one mechanism for such a diet to be related with worse visuospatial function.

This nutrient pattern is characterized by low intakes of calcium and vitamin D, antioxidants such as vitamins E and A, several B vitamins, and Ω-3 PUFA, and high intake of

Table 2. Characteristics of study subjects by tertiles of INP.

		INP Tertile			
	Total	**Lowest**	**Middle**	**Highest**	**P**
	330	**110**	**110**	**110**	
INP score, mean (SD)	0 (0.24)	-0.25 (0.19)	0.02 (0.05)	0.23 (0.12)	<0.0001
INP score, range	-1.0~ -0.76	-1.0~ -0.09	-0.08 ~0.10	0.10 ~ 0.76	
Age	**79.0 (5.76)**	**78.5 (5.4)**	**78.4 (5.5)**	**80.1 (6.2)**	**0.040**
Education	**11.04 (4.66)**	**12.17 (4.38)**	**10.96 (4.61)**	**9.99 (4.76)**	**0.002**
Female, N(%)	212 (64)	72 (66)	67 (61)	73 (66)	0.660
APOE 1 or 2 ε4, N(%)	81 (25)	26 (24)	26 (24)	29 (26)	0.860
Race/Ethnicity, N(%)					**0.008**
Whites	**108 (33)**	**49 (45)**	**35(32)**	**24 (22)**	
Blacks	**104 (32)**	**29 (26)**	**31 (28)**	**44 (40)**	
Hispanics	**109 (33)**	**29 (26)**	**39 (35)**	**41 (37)**	
Others	**9 (3)**	**3 (3)**	**5 (5)**	**1 (1)**	
BMI	27.65 (5.07)	27.02 (5.19)	27.96 (4.48)	27.96 (5.49)	0.292
Vascular Score	1.14 (0.85)	1.2 (0.93)	1.09 (0.74)	1.13 (0.86)	0.621
Language z-score	**0.34 (0.65)**	**0.46 (0.59)**	**0.35 (0.74)**	**0.22 (0.59)**	**0.024**
Memory z-score	0.14 (0.78)	0.20 (0.84)	0.13 (0.75)	0.09 (0.75)	0.570
Speed z-score	**0.21 (1.01)**	**0.33 (0.86)**	**0.29 (1.02)**	**-0.01 (1.11)**	**0.039**
Visuospatial z-score	**0.34 (0.55)**	**0.48 (0.50)**	**0.32 (0.57)**	**0.20 (0.56)**	**0.001**
Global z-score	**0.25 (0.6)**	**0.37 (0.55)**	**0.26 (0.65)**	**0.13 (0.57)**	**0.009**
ICV, cm^3	1317 (160)	1328 (167)	1322 (156)	1305 (157)	0.583
TBV, cm^3	880.2 (105)	895.7 (114)	881.3 (111)	863.6 (88)	0.076
TGMV, cm^3	**522.2 (53.2)**	**531.2 (54.8)**	**522 (56.5)**	**513.4 (46.9)**	**0.047**
TWMV, cm^3	**379.3 (57.3)**	**387.8 (60.1)**	**381.6 (59.9)**	**368.6 (50.3)**	**0.039**
TBV residual, cm^3	2.68 (67.18)	13.9 (60.44)	1.61 (71.72)	-7.46 (67.76)	0.060
TGMV residual, cm^3	**0.05 (35.5)**	**7 (33.74)**	**-1.21 (38.03)**	**-5.65 (33.7)**	**0.027**
TWMV residual, cm^3	2.44 (45.02)	9.08 (42.18)	3.81 (47.92)	-5.55 (43.95)	0.050
Mean cortical thickness, mm	2.46 (0.11)	2.47 (0.09)	2.45 (0.13)	2.45 (0.10)	0.170
WMHV, cm^3	3.6 (5.8)	2.99 (4.98)	3.43 (5.81)	4.37 (6.46)	0.201
Log_{10} (WMHV/ICV)	**-6 .0(0.69)**	**-6.07 (0.67)**	**-6.09 (0.74)**	**-5.85 (0.65)**	**0.022**

Abbreviations: apolipoprotein (APOE); intracranial volume (ICV); total brain volume (TBV); total gray matter volume (TGMV); total white matter volume (TWMV); white matter hyperintensity volume (WMHV). Values in the table show mean (SD) for all variables except for categorical variables, which are N(%). P values were from chi-squared test for categorical variables and ANOVA for continuous variables.

cholesterol which was consistent with other inflammatory dietary patterns identified using RRR with inflammatory biomarkers as response variables [12, 24]. Numerous studies have shown that certain nutrients and foods are linked to chronic low-grade inflammation. In general, long-chain ω-3 PUFAs [25], nuts [26], whole grain [27], vegetables and fruits rich in antioxidants and vitamins [28], and MeDi [29, 30] are potent in suppressing inflammatory processes and reducing inflammatory mediators, while refined grain [31], red meat [32], and dairy [33] are positively related to inflammatory biomarkers. Therefore, the INP identified in our study is in line with these nutrients' inflammatory potentials.

Table 3. Associations of the INP with brain and cognitive measures.

	Outcome variable*	Model 1		Model 2		Model 3	
		b	p	b	p	b	p
Cognition	Language	**-0.439**	**0.002**	-0.10	0.416	-0.11	0.372
	Memory	-0.287	0.094	-0.01	0.956	-0.05	0.771
	Speed/executive	**-0.560**	**0.016**	-0.29	0.194	-0.28	0.198
	Visuospatial	**-0.506**	**<0.0001**	**-0.20**	**0.041**	**-0.21**	**0.038**
	Mean cognition	**-0.455**	**<0.0001**	-0.14	0.182	-0.16	0.136
Brain	TBV (cm^3)	**-33.31**	**0.031**	**-33.44**	**0.037**	**-36.79**	**0.023**
	TGMV (cm^3)	**-22.25**	**0.005**	**-19.49**	**0.017**	**-22.90**	**0.005**
	TWMV (cm^3)	-19.54	0.053	-19.81	0.058	**-22.76**	**0.030**
	Mean cortical thickness (cm)	**-0.05**	**0.039**	-0.04	0.137	-0.04	0.116
	WMHV (cm^3)	**0.33**	**0.037**	0.17	0.286	0.22	0.177

Abbreviations: intracranial volume (ICV); total brain volume (TBV); total gray matter volume (TGMV); total white matter volume (TWMV); white matter hyperintensity volume (WMHV)

* All cognitive scores were z-scores; brain volumes were adjusted for intracranial volume using a regression model, and residuals were used in the analysis; for WMHV, the Log_{10}(WMHV/ICV) was used.

Model 1: adjusted for age. Model 2: adjusted for age, sex, education, ethnicity, caloric intake, *APOE* ε4. Model 3: adjusted for Model 2 covariates and additionally for vascular burden and BMI. All models additional adjusted for ICV for MRI outcome variables.

Bold numbers indicate significant associations.

Meanwhile, peripheral inflammatory biomarkers including CRP and IL6 are associated with aging-related brain structural findings [21, 34-36]. A recent study found increased IL8 was associated with larger WMHV in patients with AD [37]. Increased serum levels of proinflammatory biomarkers are also consistently associated with cognitive decline [9]. For example, among non-demented subjects, increased serum levels of CRP, IL6, and many other proinflammatory cytokines or adhesive molecules were associated with cognitive deficits in cross-sectional studies [38-40] or higher risk for developing AD in longitudinal studies [41-50].

Despite the strong evidence for the diet-inflammation at one hand, and inflammation-brain/cognitive ability at the other hand, very few studies have directly examined the mediation role of inflammation in the association between diet and brain measures or cognitive health. Some animal models [51-53] showed that dietary supplementation with PUFA-rich walnut, polyphenol-rich acai, or vitamin D may attenuate inflammatory signaling and improve cognition. However, the inflammatory pathway for the association between diet and brain or cognitive health has rarely been directly evaluated in human subjects except for a few studies [10, 12-14]. In our previous studies, we found that CRP did not seem to change the magnitude of the association between the healthy MeDi and incident AD [10], and the total inflammatory impact of foods was not associated with AD risk [14]. In contrast, findings from the current study are consistent with two more recent large studies [12, 13], which found diets with higher pro-inflammatory potential were associated with increased risk for AD [13] or faster decline in cognition [12]. In addition to the disparities in population characteristics, study design, and methods for defining inflammatory impact of diet, the difference in the findings might be due to a couple of other reasons. It is possible that CRP by itself may not be enough to explain the association between MeDi and AD risk. Indeed, in the current study, IL6-NP seems to have a stronger association with the cognitive health than CRP-NP. In the Whitehall II cohort study, the IL6-related dietary pattern was associated with accelerated decline in reasoning cognition [12]. IL6 also seems to be more strongly associated with neuroimaging findings than CRP [21, 36]. Secondly, inflammation may not be a key mechanism for MeDi, an *a priori* defined dietary pattern, to exert its beneficial role in preventing AD. In contrast, the RRR-derived INP was specifically designed to identify the elements in the diet that in combination can maximally capture the inflammatory profile. Therefore, the association between INP and the outcome measures can be best explained by the inherent inflammatory nature of this diet. Finally, we found that the TGMV explained a potential pathway for this INP to be related with visuospatial cognitive ability. Thus, it is possible that inflammatory processes may be more closely related to sensitive MRI measures as compared with clinical manifestations (cognitive deficits or AD diagnosis) downstream of the disease spectrum.

We found the association between INP and visuospatial cognitive score was similar between Whites and Hispanics, and so was the INP-TGMV association between Whites and Hispanics. In contrast, INP was not associated with either visuospatial cognitive score or TGMV among African-Americans. As we controlled for many demographic, clinical, vascular factors in our analyses, we figure the results were unlikely to be due to the confounding effects of these measured factors among different ethnic groups. The lack of association between this INP and cognition or brain meas-

ures in African-Americans is interesting and worth of future confirmation. We found the associations of INP with cognition in general became stronger after we limited the analyses to non-MCI subjects only, suggesting that a diet lower in inflammatory potential was associated with better cognition in the cognitively healthy older adults. Future longitudinal studies with larger sample size may help to elucidate whether a diet lower in inflammatory potential also contributes to slower decline in cognition in MCI patients.

Our study has some limitations. Although our study has the unique opportunity to simultaneously investigate the four key measures (diet, inflammation, brain MRI, and cognitive performance) that are necessary to answer our particular research question, the study population was thus limited to those with a complete set of such information. Therefore, the study population may not fully represent the source cohort population and may be prone to a potential selection bias. In addition, the selection of subjects with this complete set of variables also reduced the sample size, especially for interaction analyses and subgroup analyses, thus limiting our power for findings a relationship. Our study was a cross-sectional study and the temporal relationship cannot be completely established, neither can the longitudinal effect size be estimated. However, all these participants were dementia-free, or even without MCI in the sensitivity analysis, which minimizing the possibility that poor cognitive ability leads to an adoption of an inflammatory diet. Nevertheless, we could not completely rule out the possibility of reverse causality or confounding from early life cognitive ability, as childhood IQ might explain the relationship between dietary habits and cognitive performance in the adulthood [54]. Although CRP and IL6 were key proinflammatory biomarkers, a more comprehensive selection of inflammatory biomarkers may better capture the overall inflammatory profile of an individual [55]. Another limitation is that the nutrient patterns identified using RRR method are driven by the nutrients included in the model; therefore, the nutrient patterns may not be reproduced in other study populations, depending on whether other study populations have the same nutrients or not. Overall, the details and specificities of the findings, such as the contribution of each nutrient, the representative role of CRP and IL6 on inflammation, the nutrient pattern structure, all need to be confirmed in future studies. Nevertheless, the primary goal of the current study was to examine inflammation as a potential pathway for the relationship between dietary factors and brain or cognitive health, more than to identify a healthy or detrimental dietary pattern. Finally, although we adjusted for several key factors, we cannot completely rule out the possibility of residual confounding.

To our knowledge, this is the first study to examine the role of inflammation-related diet and neuroimaging markers, and to examine the mediation role of brain health in the relationship of this diet and cognitive abilities. Considering the increasingly diverse US population [17], our study population has an advantage that it is composed of multiple ethnic groups. We controlled a wide range of potential confounders. The dementia and MCI diagnoses were made at consensus meeting according to standard research criteria, allowing us to perform the study among a dementia-free study sample as well as a sensitivity analysis in non-MCI healthy older adults. Our study is also novel in terms of nutrient pattern construction, by using RRR method which is a powerful tool to test dietary hypotheses based on etiology [2, 4].

CONCLUSION

Aging is accompanied by systemic chronic low-grade inflammation such as increases levels of inflammatory mediators in the peripheral [56] as well as exaggerated neuroinflammation facilitated by microglia priming in the brain [57], placing older adults at a higher risk of brain and cognitive decline. Our study suggests that, if the systemic environment is favorable, such as low systemic inflammation by following a healthy diet, individuals may have less AD-related brain and cognitive deficits.

LIST OF ABBREVIATIONS

APOE	=	Apolipoprotein
CRP	=	C-reactive protein
IL6	=	Interleukin-6
ICV	=	Intra-cranial volume
MRI	=	Magnetic resonance imaging
PUFAs	=	Poly-unsaturated fatty acids
RRR	=	Reduced rank regression
TBV	=	Total brain volume
TGMV	=	Total gray matter volume
TWMV	=	Total white matter volume
WHICAP	=	Washington Heights/Hamilton Heights Inwood Columbia Aging Project
WMHV.	=	White matter hyperintensity volume

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Columbia University Institutional Review Board.

HUMAN AND ANIMAL RIGHTS

No animal were used in this research. all humans research procedures followed were in accordance with the standards set forth in the *Declaration of Helsinki* principles of 1975, as revised in 2008 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

CONSENT FOR PUBLICATION

All participants provided written informed consent.

CONFLICT OF INTEREST

Dr. Gu reports no disclosures relevant to the study.

Dr. Manly serves on the Medical and Scientific Advisory Board of the Alzheimer's Association. Her scientific work is funded by grants from NIH and the Alzheimer's Association.

Dr. Mayeux reports no disclosures relevant to the study.

Dr. Brickman is on the Scientific Advisory Boards and serves as a paid consultant for ProPhase, LLC, and Keystone

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

REFERENCES

[1] Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimer's Dementia 11(6): 718-26 (2015).

[2] Gu Y, Scarmeas N. Dietary patterns in Alzheimer's disease and cognitive aging. Curr Alzheimer Res 8(5): 510-9 (2011).

[3] Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 59(6): 912-21 (2006).

[4] Gu Y, Nieves JW, Stern Y, Luchsinger JA, Scarmeas N. Food combination and Alzheimer's disease risk: a protective diet. Arch Neurol 67(6): 699-706 (2010).

[5] Gu Y, Brickman AM, Stern Y, Habeck CG, Razlighi QR, Luchsinger JA, *et al*. Mediterranean diet and brain structure in a multiethnic elderly cohort. Neurology 85(20): 1744-51 (2015).

[6] Gu Y, Vorburger RS, Gazes Y, Habeck CG, Stern Y, Luchsinger JA, *et al*. White matter integrity as a mediator in the relationship between dietary nutrients and cognition in the elderly. Ann Neurol 79(6): 1014-25 (2016).

[7] Jack CR, Jr., Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, *et al*. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 9(1): 119-28 (2010).

[8] Gardener SL, Rainey-Smith SR, Martins RN. Diet and inflammation in Alzheimer's disease and related chronic diseases: a review. J Alzheimer's Dis 50(2): 301-34 (2016).

[9] Eikelenboom P, Hoozemans JJ, Veerhuis R, van Exel E, Rozemuller AJ, van Gool WA. Whether, when and how chronic inflammation increases the risk of developing late-onset Alzheimer's disease. Alzheimer's Res Ther 4(3): 15 (2012).

[10] Gu Y, Luchsinger JA, Stern Y, Scarmeas N. Mediterranean diet, inflammatory and metabolic biomarkers, and risk of Alzheimer's disease. J Alzheimer's Dis 22(2): 483-92 (2010).

[11] Hoffmann K, Schulze MB, Schienkiewitz A, Nothlings U, Boeing H. Application of a new statistical method to derive dietary patterns in nutritional epidemiology. Am J Epidemiol 159(10): 935-44 (2004).

[12] Ozawa M, Shipley M, Kivimaki M, Singh-Manoux A, Brunner EJ. Dietary pattern, inflammation and cognitive decline: The Whitehall II prospective cohort study. Clinical Nutrition (Edinburgh, Scotland). 36(2): 506-12 (2017).

[13] Hayden KM, Beavers DP, Steck SE, Hebert JR, Tabung FK, Shivappa N, *et al*. The association between an inflammatory diet and global cognitive function and incident dementia in older women: the Women's Health Initiative Memory Study. Alzheimer's Dementia 213(11): 1187-96 (2017).

[14] Gu Y, Nieves JW, Luchsinger JA, Scarmeas N. Dietary inflammation factor rating system and risk of Alzheimer disease in elders. Alzheimer Dis Assoc Disord 25(2): 149-54 (2011).

[15] Stern Y, Andrews H, Pittman J, Sano M, Tatemichi T, Lantigua R, *et al.* Diagnosis of dementia in a heterogeneous population. Development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. Arch Neurol 49(5): 453-60 (1992).

[16] Manly JJ, Bell-McGinty S, Tang MX, Schupf N, Stern Y, Mayeux R. Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. Arch Neurol 62(11): 1739-46 (2005).

[17] Brickman AM, Schupf N, Manly JJ, Luchsinger JA, Andrews H, Tang MX, *et al*. Brain morphology in older African Americans, Caribbean Hispanics, and whites from northern Manhattan. Arch Neurol 65(8): 1053-61 (2008).

[18] Luchsinger JA, Tang MX, Siddiqui M, Shea S, Mayeux R. Alcohol intake and risk of dementia. J Am Geriatr Soc 52(4): 540-6 (2004).

[19] Luchsinger JA, Tang MX, Shea S, Mayeux R. Caloric intake and the risk of Alzheimer disease. Arch Neurol 59(8): 1258-63 (2002).

[20] Luchsinger JA, Tang MX, Shea S, Mayeux R. Antioxidant vitamin intake and risk of Alzheimer disease. Arch Neurol 60(2): 203-8 (2003).

[21] Gu Y, Vorburger R, Scarmeas N, Luchsinger JA, Manly JJ, Schupf N, *et al*. Circulating inflammatory biomarkers in relation to brain structural measurements in a non-demented elderly population. Brain, Behav Immun 65: 150-60 (2017).

[22] Brickman AM, Zahodne LB, Guzman VA, Narkhede A, Meier IB, Griffith EY, *et al*. Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence. Neurobiol Aging 36(1): 27-32 (2015).

[23] Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Meth 40(3): 879-91 (2008).

[24] Schulze MB, Hoffmann K, Manson JE, Willett WC, Meigs JB, Weikert C, *et al*. Dietary pattern, inflammation, and incidence of type 2 diabetes in women. Am J Clin Nut 82(3): 675-84; quiz 714-5 (2005).

[25] Ticinesi A, Meschi T, Lauretani F, Felis G, Franchi F, Pedrolli C, *et al*. Nutrition and inflammation in older individuals: focus on vitamin d, n-3 polyunsaturated fatty acids and whey proteins. Nutrients 8(4): 186 (2016).

[26] Yu Z, Malik VS, Keum N, Hu FB, Giovannucci EL, Stampfer MJ, *et al*. Associations between nut consumption and inflammatory biomarkers. Am J Clin Nut 104(3): 722-8 (2016).

[27] Vitaglione P, Mennella I, Ferracane R, Rivellese AA, Giacco R, Ercolini D, *et al*. Whole-grain wheat consumption reduces inflammation in a randomized controlled trial on overweight and obese subjects with unhealthy dietary and lifestyle behaviors: role of polyphenols bound to cereal dietary fiber. Am J Clin Nut 101(2): 251-61 (2015).

[28] Root MM, McGinn MC, Nieman DC, Henson DA, Heinz SA, Shanely RA, *et al*. Combined fruit and vegetable intake is correlated with improved inflammatory and oxidant status from a cross-sectional study in a community setting. Nutrients 4(1): 29-41 (2012).

[29] Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, *et al*. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 292(12): 1440-6 (2004).

[30] Estruch R, Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ruiz-Gutierrez V, Covas MI, *et al*. Effects of a mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med 145(1): 1-11 (2006).

[31] Masters RC, Liese AD, Haffner SM, Wagenknecht LE, Hanley AJ. Whole and refined grain intakes are related to inflammatory protein concentrations in human plasma. J Nutrition 140(3): 587-94 (2010).

[32] Kim Y, Keogh JB, Clifton PM. Effects of two different dietary patterns on inflammatory markers, advanced glycation end products and lipids in subjects without type 2 diabetes: a randomised crossover study. Nutrients 9(4): pii: E336 (2017).

[33] Baer DJ, Judd JT, Clevidence BA, Tracy RP. Dietary fatty acids affect plasma markers of inflammation in healthy men fed con-

trolled diets: a randomized crossover study. Am J Clin Nutr 79(6): 969-73 (2004).
[34] Frodl T, Amico F. Is there an association between peripheral immune markers and structural/functional neuroimaging findings? Prog Neuro-psychopharmacol Biol Psychiat 48: 295-303 (2014).
[35] Marsland AL, Gianaros PJ, Kuan DC, Sheu LK, Krajina K, Manuck SB. Brain morphology links systemic inflammation to cognitive function in midlife adults. Brain, Behav Immun 48: 195-204 (2015).
[36] Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: the 3C-Dijon Study. Neurology 78(10): 720-7 (2012).
[37] Zhu Y, Chai YL, Hilal S, Ikram MK, Venketasubramanian N, Wong BS, *et al*. Serum IL-8 is a marker of white-matter hyperintensities in patients with Alzheimer's disease. Alzheimer's Dementia (Amsterdam, Netherlands) 7: 41-7 (2017).
[38] Trollor JN, Smith E, Agars E, Kuan SA, Baune BT, Campbell L, *et al*. The association between systemic inflammation and cognitive performance in the elderly: the Sydney Memory and Ageing Study. Age (Dordrecht, Netherlands) 34(5): 1295-308 (2012).
[39] Wright CB, Sacco RL, Rundek T, Delman J, Rabbani L, Elkind M. Interleukin-6 is associated with cognitive function: the Northern Manhattan Study. J Stroke Cerebrovasc Dis 15(1): 34-8 (2006).
[40] Baune BT, Ponath G, Golledge J, Varga G, Arolt V, Rothermundt M, *et al*. Association between IL-8 cytokine and cognitive performance in an elderly general population--the MEMO-Study. Neurobiol Aging 29(6): 937-44 (2008).
[41] Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, *et al*. Inflammatory proteins in plasma and the risk of dementia: the rotterdam study. Arch Neurol 61(5): 668-72 (2004).
[42] Tan ZS, Beiser AS, Vasan RS, Roubenoff R, Dinarello CA, Harris TB, *et al*. Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. Neurology 68(22): 1902-8 (2007).
[43] Ravaglia G, Forti P, Maioli F, Chiappelli M, Montesi F, Tumini E, *et al*. Blood inflammatory markers and risk of dementia: The Conselice Study of Brain Aging. Neurobiol Aging 28(12): 1810-20 (2007).
[44] Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol 52(2): 168-74 (2002).
[45] Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, *et al*. The Metabolic Syndrome, Inflammation, and Risk of Cognitive Decline. JAMA 292(18): 2237-42 (2004).
[46] Dik MG, Jonker C, Hack CE, Smit JH, Comijs HC, Eikelenboom P. Serum inflammatory proteins and cognitive decline in older persons. Neurology 64(8): 1371-7 (2005).
[47] Weaver JD, Huang MH, Albert M, Harris T, Rowe JW, Seeman TE. Interleukin-6 and risk of cognitive decline: macArthur studies of successful aging. Neurology 59(3): 371-8 (2002).
[48] Laurin D, David Curb J, Masaki KH, White LR, Launer LJ. Midlife C-reactive protein and risk of cognitive decline: a 31-year follow-up. Neurobiol Aging 30(11): 1724-7 (2009).
[49] Dlugaj M, Gerwig M, Wege N, Siegrist J, Mann K, Brocker-Preuss M, *et al.* Elevated levels of high-sensitivity C-reactive protein are associated with mild cognitive impairment and its subtypes: results of a population-based case-control study. J Alzheimer's Dis 28(3): 503-14 (2012).
[50] Elderkin-Thompson V, Irwin MR, Hellemann G, Kumar A. Interleukin-6 and memory functions of encoding and recall in healthy and depressed elderly adults. Am J Geriatr Psychiatry 20(9): 753-63 (2012).
[51] Carey AN, Miller MG, Fisher DR, Bielinski DF, Gilman CK, Poulose SM*, et al.* Dietary supplementation with the polyphenol-rich acai pulps (Euterpe oleracea Mart. and Euterpe precatoria Mart.) improves cognition in aged rats and attenuates inflammatory signaling in BV-2 microglial cells. Nutr Neurosci 20(4): 238-45 (2017).
[52] Briones TL, Darwish H. Vitamin D mitigates age-related cognitive decline through the modulation of pro-inflammatory state and decrease in amyloid burden. J Neuroinflamm 9: 244 (2012).
[53] Fisher DR, Poulose SM, Bielinski DF, Shukitt-Hale B. Serum metabolites from walnut-fed aged rats attenuate stress-induced neurotoxicity in BV-2 microglial cells. Nutr Neurosci 20(2): 103-9 (2017).
[54] Corley J, Starr JM, McNeill G, Deary IJ. Do dietary patterns influence cognitive function in old age? International psychogeriatrics/IPA. 25(9): 1393-407 (2013).
[55] Baune BT, Ponath G, Rothermundt M, Roesler A, Berger K. Association between cytokines and cerebral MRI changes in the aging brain. J Geriatr Psychiatry Neurol 22(1): 23-34 (2009).
[56] Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol 39(5): 687-99 (2004).
[57] Perry VH, Holmes C. Microglial priming in neurodegenerative disease. Nat Rev Neurol 10(4): 217-24 (2014).

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